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主　論　文　の　要　旨

論文題目　Evaluation of morphological and hemodynamic biomarkers to assess rupture risk of intracranial aneurysms using magnetic resonance fluid dynamics and computational fluid dynamics

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論　文　内　容　の　要　旨

Introduction

Intracranial aneurysms are pathological dilatations of the arterial walls and an estimated overall prevalence of 3.2% has been reported for a non-comorbid population. Recent advancements in neurovascular imaging and treatment techniques have increased the detection and thereby treatment of intracranial aneurysms. However, treatment of unruptured intracranial aneurysms carries the risk of associated morbidity and mortality rates regardless of their benefits. Hence deciding which aneurysms should undergo treatment is of vital importance.

Hemodynamics, which can be evaluated using either magnetic resonance fluid dynamics (MRFD) utilizing 3D cine phase-contrast MR imaging or computational fluid dynamics (CFD), has been proposed by many researchers as a causative factor in aneurysm pathophysiology as well as in the mechanisms of growth and rupture. However, all the studies, which have investigated morphological and hemodynamic parameters to assess rupture risk of intracranial aneurysms are based on CFD analysis and none of these studies had used patient specific inflow-outflow boundary conditions for the analysis which is a major limitation. In addition, to our knowledge, no rigorous intracranial aneurysm rupture risk assessment study has been reported that utilizes MRFD analysis with representative larger samples rather than case reports. Thus, the aim of the present study was to evaluate in-vivo hemodynamic and morphological biomarkers of intracranial aneurysms, using MRFD and patient specific CFD in order to assess the risk of rupture.

Methods

This study was approved by the institutional review board of Nagoya University Graduate School of Medicine and informed consent had been taken from the patients whose image data were utilized. Forty-eight intracranial aneurysms (10 ruptured, 38 unruptured) were analyzed using MRFD and patient specific MR-based CFD.

Study subjects

Our data-base consists of 297 intracranial aneurysms of 203 patients who had been followed up after the initial diagnosis. 3D time-of-flight magnetic resonance angiography (3D TOF MRA) and 3D cine phase-contrast magnetic resonance imaging (3D cine PC MRI) data of intracranial aneurysms which had been followed up at our three affiliated institutes contributing to our data-base from 2005 to 2018 were reviewed in the current investigation. Saccular intracranial aneurysms, consisting both lateral wall and bifurcation type were included in the study. Of 297 aneurysms, 11 had ruptured during the follow up. From these ruptured cases, 7 aneurysms had undergone 3D cine PC MRI before rupture enabling the analysis of pre-rupture status exclusively while 4 cases had undergone 3D cine PC MRI immediately or few days after rupture. Careful inspection was carried out to confirm vasospasm or any geometric change caused by the rupture for these 4 cases. As a result, 3 cases were included in the study and 1 case was excluded due to the presence of vasospasm. Thus 10 ruptured aneurysms were selected to “ruptured group”. Average time duration from image acquisition to rupture date was 56 months for the aneurysms which ruptured during follow-up and average time duration from aneurysm rupture to imaging date was 3 days for the aneurysms without follow-up before rupture. Inclusion criteria for the “unruptured group”, which consisted of aneurysms that did not rupture during the follow-up, were the aneurysms located in similar sites as the ruptured group with no evidence of SAH and with at least 20 months’ follow-up time. This resulted in 182 aneurysms. Subsequent exclusion criteria were the aneurysms which underwent endovascular treatment (109), giant intracranial aneurysms (size >10mm) or aneurysms of size less than 3mm (27), aneurysms with arteriosclerotic changes (2), aneurysms with improper velocity encoding (VENC) settings or narrow field of view (FOV) (6). Accordingly, 144 aneurysms had to be excluded from the “unruptured group”, resulting in 38 aneurysms which met all the inclusion and exclusion criteria.

Imaging equipment

1.5T MR scanner with 8-channel neurovascular array coil and two 3T MR scanners with 8-channel and 12-channel neurovascular array coils were utilized in image acquisition.

MRFD Analysis

Blood flow analysis software, Flova, (Renaissance Technology Corporation, Hamamatsu, Japan) was utilized for MRFD analysis. First patient-specific vascular geometries were obtained from 3D TOF MRA data. Next 3D velocity vectors obtained from 3D cine PC MRI were loaded over the extracted vessel geometry using Flova. Once the optimum registration of 3D flow velocity vectors over the vessel geometry was attained morphological and hemodynamic biomarker calculations were carried out.

CFD analysis

ICEM CFD version 14.5 (ANSYS, Canonsburg, Pennsylvania, USA) was utilized to create tetrahedral meshes of 3D vascular geometries. CFD solver software CFX version14.5 (ANSYS, Canonsburg, Pennsylvania, USA) was used to compute velocity biomarkers by solving Navier-Stokes equation. Volume flow rate obtained from the MRFD analysis was used as the patient specific boundary condition. Two cardiac cycles were simulated and the results of the second cycle were taken for the calculation of hemodynamic biomarkers to ensure numeric stability. Hemodynamic biomarker calculation was proceeded using CFD-Post 14.5 (ANSYS, Canonsburg, Pennsylvania, USA).

Morphological biomarkers

Six morphological biomarkers denoting aneurysm size and shape measures, namely size, volume, aspect ratio, size ratio, presence of blebs and nonsphericity index (NSI) were investigated in this study.

Hemodynamic biomarkers

Four main hemodynamic parameters were investigated in this study. One parameter, the inflow concentration index (ICI), was chosen as a velocity biomarker. The other 3 parameters were derivatives of wall sheer stress (WSS), which is defined as the multiplication of fluid viscosity and shearing velocity of neighboring vascular wall. WSS related parameters evaluated in this study were time averaged wall shear stress (TAWSS), oscillatory shear index (OSI) and relative residence time (RRT). TAWSS, OSI and RRT were further analyzed to obtain spatial average, spatial maximum and spatial minimum values.

Statistical Analysis

IBM SPSS Statistics (version 25) was used for the statistical analysis. Unpaired Student's t-test or Mann-Whitney U test were conducted as univariate analysis to detect any significant differences in the biomarkers between the ruptured group and the unruptured group. Receiver operating characteristic (ROC) analysis was performed for the selected statistically significant biomarkers, and

area under the curve (AUC) values and optimal threshold using Yuden index were calculated for them. Logistic regression analysis (using backward stepwise elimination method) was also conducted as multivariate analysis. Correlations between MRFD and CFD based hemodynamic biomarkers were assessed by Spearman's correlation coefficients. All reported p-values were two-sided, and p-values below 0.05 were considered to indicate statistical significance for all statistical tests.

Results

48 intracranial aneurysms categorized as ruptured (10 aneurysms) and unruptured (38 aneurysms) were included in the analysis. Ruptured group consisted of 1 anterior communicating artery (AComA) aneurysm, 1 middle cerebral artery (MCA) aneurysm, 3 internal carotid-posterior communicating artery (ICPComA) aneurysms, 1 internal carotid-anterior choroidal artery (ICAnt.ChoA) aneurysm, 1 basilar artery tip (BA Tip) aneurysm, 2 basilar artery-superior cerebellar artery (BASCA) aneurysms and 1 vertebral artery-posterior inferior cerebellar artery (VAPICA) aneurysm. Unruptured group comprised 7 AComA aneurysms, 16 MCA aneurysms, 7 ICPComA aneurysms, 2 ICAnt.ChoA aneurysms, 5 BA Tip aneurysms and 1 BASCA aneurysm. With respect to the clinically known risk factors for aneurysm rupture, our study did not reveal any statistical significance for any of the assessed risk factors.

In the morphological biomarker analysis, aneurysm size ($p = 0.021$), volume ($p = 0.035$) and size ratio ($p = 0.039$) were found to be statistically significantly different between the ruptured and unruptured aneurysms, while aspect ratio and NSI were not statistically significantly different. With respect to the presence of blebs, 15 aneurysms with blebs were found in the unruptured group and 5 aneurysms presented blebs in the ruptured group. Thus, Fishers exact test could not reveal a statistical significance ($p= 0.721$) for the presence of blebs in discriminating aneurysm rupture.

In hemodynamic biomarker analysis, MRFD results indicated that ruptured aneurysms had higher OSI (OSI.max, $p = 0.037$) and higher RRT (RRT.ave, $p = 0.035$; RRT.max, $p = 0.054$) compared to unruptured aneurysms. Correspondingly CFD analysis demonstrated significant differences for both average and maximum OSI (OSI.ave, $p = 0.008$; OSI.max, $p = 0.01$) and maximum RRT (RRT.max, $p = 0.045$). However, the other hemodynamic biomarkers (ICI and TAWSS) were not statistically significantly different either in MRFD or in CFD analysis.

ROC analysis revealed area under the curve (AUC) values greater than 0.7 for all significant morphological and hemodynamic biomarkers. In the multivariate analysis, with respect to the morphological biomarkers, the volume of aneurysm (*An.Vol*) [OR, 1.015; 95% CI, 1.004-1.026] was the only significant predictor of aneurysm rupture which was retained in the model (AUC, 0.718;

95% CI, 0.491–0.946) and its odds of aneurysm rupture (Odd_M) was estimated to be;

$$Odd_M = e^{0.015\,(An.Vol)-2.652}$$

In the hemodynamic biomarkers derived from the CFD analysis, average OSI (*OSI.ave*) [OR, $1.942e^{+32}$; 95% CI, 8706.389-$4.333e^{+60}$] was the only significant predictor of aneurysm rupture which was retained in the logistic regression model (AUC, 0.774; 95% CI, 0.586–0.961) and its odds of aneurysm rupture (Odd_H) was estimated to be;

$$Odd_H = e^{74.347\,(OSI.ave)-2.775}$$

However, there were no any significant predictors of aneurysm rupture among the MRFD based hemodynamic biomarkers with respect to multivariate regression analysis.

Spearman's rank correlation coefficients revealed strong positive monotonic correlations between MRFD and CFD for ICI, and moderate positive monotonic correlations for TAWSS.ave, TAWSS.min, OSI.ave, OSI.max, RRT.ave, and RRT.max. The other biomarkers were unable to reveal such significant correlations. However, all the biomarkers which were found to be significant risk factors for aneurysm rupture showed moderate correlations between MRFD and CFD.

Conclusion

Both morphological and hemodynamic biomarkers have significant influence on intracranial aneurysm rupture. Aneurysm size, volume, size ratio, oscillatory shear index and relative residence time could be potential biomarkers to assess aneurysm rupture risk where aneurysm volume and oscillatory shear index are the most significant predictors of aneurysm rupture.